Symposium: Review Article

Myocardial disease, anemia and heart failure

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Abstract Many patients with congestive heart failure (CHF) fail to respond to maximal CHF therapy and progress to end stage CHF with many hospitalizations, very poor quality of life, end stage renal failure, or die of cardiovascular complications within a short time. One factor that has generally been ignored in many of these patients is the fact that they are often anemic. The anemia is due mainly to renal failure but also to the inhibitory effects of cytokines on the bone marrow. Anemia itself may further worsen the cardiac function and make the patients resistant to standard CHF therapies. Indeed anemia has been associated with increased severity of CHF, increased hospitalization, worse cardiac function and functional class, higher doses of diuretics, worsening of renal function and reduced quality of life. In both controlled and uncontrolled studies the correction of the anemia with erythropoietin (EPO) and oral or IV iron is associated with improvement in all these parameters. EPO itself may also play a direct role in improving the heart unrelated to the improvement of the anemia. Anemia may also play a role in the worsening of coronary heart disease even without CHF.

Key words heart failure; renal failure; anemia; erythropoietin; iron

Introduction

Congestive heart failure (CHF) is a major health burden in the western world.1,4 Some recent data suggest that almost 1 in 3 people who have reached the age of 55 will develop CHF during their remaining life span.1 The burden of CHF is particularly high in the elderly—about 80% of new diagnoses are in patients age 65 and older—the mean age of CHF patients being about 74.1,4 Despite many advances in the treatment of CHF, mortality is still very high, reaching 30-40% at one year in some studies.1,4 Although most deaths are due to cardiac or cardiovascular causes, a substantial number of patients progress to end stage renal disease (ESRD) which may be partially related to the progressive CHF.1,4 In addition many remain severely symptomatic despite optimal CHF therapy including treatment with angiotensin converting enzyme inhibitors (ACEIs), beta blockers, angiotensin receptor blockers (ARBs), and aldospironone.1,5

Anemia is frequently seen in CHF patients.3,16 Is it possible that this anemia is an important contributor to this failure to respond to standard CHF treatment? Anemia (as defined by us as a hemoglobin (Hb) of less than 12g/dl) has been found in our own studies in about half the cases of CHF seen in our CHF outpatient clinic10 and in about half the CHF cases requiring hospitalization.11 Anemia in CHF has been associated with increased mortality, increased hospitalization, and a greater severity of CHF compared to non-anemic CHF patients.2,12 That anemia may actually be contributing to the severity of the CHF is suggested by several controlled and uncontrolled studies which we and others have carried out in which correction of the anemia in severe resistant CHF patients by subcutaneous (sc) erythropoietin (EPO) used together with IV iron10,13,15,19 or oral iron13,20 has been associated with an improvement in functional capacity and cardiac function,10,13,18 a reduction in hospitalizations,10,13,15,19,20 a stabilization or improvement in renal function,10,13,14,16,18,20 a reduction in the dose of diuretics needed10,13,17,18 and an improvement in the quality of life.17

How common are anemia and CKI in CHF?

Many studies in addition to our own have appeared recently which have studied this relationship between anemia and CHF.3,12 Analysis of these studies suggests that about 40% of patients with CHF have a Hb below 12g/dl. In the many studies that have examined the relationship between CHF and the level of mean Hb or hematocrit (Hct) and/or the prevalence of anemia in CHF patients, there is a very wide variation in prevalence of anemia—from 2.72% to 61%.7,12 Why the enormous variation? Examination of these studies shows that the anemia was generally more common in the elderly, in diabetics and in those with more severe renal damage or more severe CHF. It was also more common in those who were hospitalized than in those treated in the community, and more common in those in whom the anemia was defined as a Hb...
How does anemia cause CHF?

It has been known for years that anemia, if severe enough, can cause heart failure even in normal individuals. Indeed one recent study of over 1 million elderly US Medicare patients showed that anemia was an independent predictor of the development of CHF over a one year period. The tissue hypoxia and peripheral vasodilation present in anemia causes a lowering of blood pressure, leading to an increased sympathetic response, which leads to tachycardia, increased stroke volume, renal vasoconstriction, reduced renal blood flow, and salt and water retention (Fig. 1). This will lead to an increase in ECF including an increase in plasma volume. The reduced renal blood flow will also cause an increased secretion of renin, angiotensin, aldosterone and anti diuretic hormone (ADH), further augmenting the renal vasoconstriction and salt and water retention, and further increasing the ECF plasma volume. In addition norepinephrine, renin, angiotensin, and aldosterone are all toxic to renal, cardiac, endothelial cells and other cells. The tachycardia and increased stroke volume can eventually lead to ventricular dilation and hypertrophy.

Abnormalities associated with anemia in CHF

Compared to CHF patients without anemia, the presence of anemia in CHF patients has been associated with many abnormalities (7-12) including higher mortality, more hospitalizations, longer hospitalizations, higher hospitalization costs, a worse New York Heart Association (NYHA) functional class, lower left ventricular systolic function (as judged by a lower left ventricular ejection fraction (LVEF), and worse ventricular diastolic function, lower exercise capacity, reduced oxygen utilization during peak exercise (MVo2), lower quality of life, higher serum beta natriuretic peptide (BNP) levels, (which suggest more severe CHF), elevated plasma volume and total body water, lower red cell volume and more severe peripheral edema, lower blood pressure, higher heart rate, poorer peripheral perfusion, higher venous filling pressures, higher pulmonary capillary wedge pressures, and a greater resistance to therapy as judged by the need for higher doses of diuretics and digoxin. Anemia in CHF is also often associated with lower renal function and more rapid deterioration of renal function, and with signs of malnutrition such as a low body mass index, low serum albumin, low serum total protein, and low serum cholesterol. The anemia and malnutrition seen in CHF may be partly caused by increased inflammatory cytokines such as tumor necrosis factor alpha (TNF/Â) and interleukin 6 (IL, 6), all signs of inflammation.

It is ironic that something as simple and as simply measured as Hb may be as powerful a predictor of cardiovascular events in CHF as LVEF, cardiac catheterization variables such as left and right ventricular pressures, BNP, exercise capacity and MVo2.

Is anemia actually causing the worsening of the CHF?

Results of correcting the anemia

Does the anemia actually contribute to the worsening of the CHF or is it just an innocent bystander, merely a marker of more severe CHF? One way of finding out is to actually treat the anemia and see if this improves the CHF.

In both uncontrolled and controlled studies we showed that when the anemia is corrected to a Hb of 12.0 to 13.5 g/dl by subcutaneous (sc) iron EPO and IV iron (ferric
sucrose- Venofer- Vifor Int), the CHF improved, as evidenced by improvement of the New York Heart Association (NYHA) functional class, increased LVEF, reduced number and days of hospitalization, reduced doses of oral and IV furosemide required, and improved self assessed shortness of breath and fatigue. In the uncontrolled studies,\textsuperscript{13,14}\textsuperscript{15} we also found that the creatinine clearance (CCR), that had been falling at a rate of about 1 ml/min/month before the anemia was corrected, stabilized after correction of the anemia. All these patients had been under cardiologists’ care before we intervened to treat the anemia and had been on maximally tolerated doses of all the recommended CHF medications but were still resistant to therapy and were highly symptomatic. In the controlled study, the group in which the anemia was treated had no change in mean serum creatinine whereas in the untreated group the mean serum creatinine levels increased significantly.\textsuperscript{16} In addition one quarter of the patients in the controlled group died – all due to severe progressive CHF, whereas none died in the treatment group in which the anemia had been corrected.

In a randomized placebo controlled study of 22 patients with anemia and very severe CHF\textsuperscript{17} Mancini et al evaluated the use of sc EPO and oral iron over a 3 month period. Exercise duration, the distance walked in 6 minutes, peak oxygen utilization during maximal exercise (MVO\textsubscript{2}), and the quality of life all improved in the treated group (whose mean Hb increased from 11.0 to 14.3 g/dl) and either stayed the same or worsened in the placebo group. The degree of improvement in MVO\textsubscript{2} was proportional to the degree of change in the Hb. This is important since MVO\textsubscript{2} is an important prognostic indicator for CHF survival.\textsuperscript{18} In another study by the same group the anemia was found to be associated with a reduced red cell mass in the majority of cases and with an increased plasma volume (PV) in the rest.\textsuperscript{19} Correction of the anemia reduced the PV to normal and increased the red cell mass.\textsuperscript{18}

In a preliminary US study,\textsuperscript{17} 84 CHF patients with anemia (Hb <12g/dl) and CKI (serum creatinine ≥1.5mg/dl) were treated with IV iron (ferric gluconate-Ferlecit) and Epoetin alpha over a period of up to 15 months. By the end of the treatment period, compared to a similar period of time before the treatment, 37% had a decrease in serum creatinine and 30% had a decreased oral diuretic dose. The number of admissions to hospitals had decreased by 43% and the number of hospital days had decreased by 33%.

In another preliminary US study,\textsuperscript{17} 81 patients with predominantly NYHA III and IV CHF and anemia (Hb<11g/ dl) were treated with EPO and oral iron. Mean follow up was 438±336 days. The mean initial BUN was 51±31mg/dl and the mean initial serum creatinine was 2.1±1.8mg/dl. The Hb increased from a mean of 9.9±1.1 before to 11.7±1.7g/dl after treatment. The mean BUN fell to 38±23 mg/dl. The number of hospital days compared to an equal period before treatment fell by 50%.

In yet another preliminary study\textsuperscript{20} 10 patients with severe CHF and a Hb of less than 12g/dl were treated for a mean of 5.0±2.7 months with EPO and IV iron. All were receiving maximal medication for CHF. The results were compared to 13 similar patients in whom the anemia was not treated. The Hb in the treated group increased from 10.2± to 13.7±1.2 g/dl but remained unchanged at 10.6±0.9 in the untreated group. Compared to the untreated group, correction of the anemia was associated with a marked improvement in NYHA (1.7 in the treated vs 3.2 in the untreated), 90.3% less episodes of severe CHF, 88.7% less hospitalizations, and a 61% reduction in the need for IV diuretics. The serum creatinine was 1.4±0.2 mg/dl in the treated and 1.7 ±0.7 mg/dl in the non treated (not significant).

Another argument in favor of anemia being partly responsible for the worsening of heart failure is the effect anemia has on BNP. BNP is now used for both the diagnosis of CHF and for assessing prognosis.\textsuperscript{21} It reflects the volume, stretch and pressure in the ventricles. Studies in CHF have found that the BNP levels in cardiac patients both with and without CHF\textsuperscript{22,23} were related inversely to Hb levels – the lower the Hb the higher the BNP. In patients with anemia but without cardiac disease\textsuperscript{24} atrial natriuretic peptide (ANP) was also elevated, and when the anemia was corrected the ANP returned to normal. In one study anemia was found to be a better predictor of long-term survival in CHF than the BNP level.\textsuperscript{25} All these data clearly suggest that anemia indeed does play a role in the worsening of CHF, but large randomized placebo-controlled studies are needed to confirm this, and these are indeed currently in progress.

Can treatment of anemia prevent CHF in CKI patients?

Anemia in CKI is associated with an increase in hospitalizations.\textsuperscript{26,27} Collins and his associates have shown that the consistent use of EPO in CKI patients in the 2 years before dialysis is associated with reduced rates of hospitalization for CHF and other heart diseases before dialysis and with less CHF and hospitalizations after onset of dialysis.\textsuperscript{28,29} In a similar study, the PRESAM study carried out in Europe and elsewhere, the use of EPO in the pre-dialysis period was associated with a lower incidence of CHF, angina pectoris and MI during this period.\textsuperscript{30} The mortality rate after dialysis was started has also been shown to be lower in those who received EPO in the predialysis period\textsuperscript{31,32} as is the hospitalization rate.\textsuperscript{33,34}

The clinical improvement in our own studies of severe CHF patients, most of whom also had CKI,\textsuperscript{35} suggests that the multifaceted approach we used, with close cooperation between cardiologists and nephrologists, and maximal therapy of the CHF and the anemia, seems to prevent the progression of both the cardiac and the renal complications of CHF.

What is the effect of this anemia on severity of CHF and on mortality?

Many studies have examined the relationship between anemia, CHF severity, and mortality.\textsuperscript{36,37} Of 25 studies that looked at the relationship between severity of CHF and anemia, 20 (80%) showed that the presence of anemia was associated with a more severe degree of CHF as judged by NYHA functional class.\textsuperscript{38} Of 46 studies that examined the relationship between mortality and anemia in CHF, 44 (95.7%) showed a positive relationship.\textsuperscript{36,37} In many of these studies these relationships between anemia and CHF were still statistically
The additive effects of CHF, CKI and anemia

In a study of over 1 million US Medicare elderly patients it was found that CHF, CKI and anemia are additive in increasing mortality and the risk of developing ESRD. It is not perhaps surprising that anemia and CHF are such a lethal combination considering the fact that both cause hypotension which activates the sympathetic and renin, angiotensin and aldosterone system (RAAS) causing tachycardia and increased cardiac work, reduced renal function, increased salt and water absorption, increased extracellular fluid and increased plasma volume. In addition, all three conditions, CHF and CKI as well as anemia, are associated with an increase in four toxic mechanisms: an increase in sympathetic activity, an increase in the activity of the RAAS, an increase in oxidative stress and an increase in inflammation. Even more worrisome is the fact that all four of these toxic mechanisms not only attack and destroy body cells but that they also each activate each other. Thus the sympathetic system activates the other three, as do all the other three mechanisms. This suggests that the only way to improve CHF and CKI is by a broad-based attack on all four of the mechanisms - something that we do when we use ACEI/ARBs, beta blockers and aldosterone inhibitors as well as control the anemia.

The effect of anemia on hospitalization, mortality and hospital expenses in CHF

Nine studies that examined the relationship between anemia and the number and/or duration of hospitalizations all found a significant relationship. Kosiborod et al found that a 1% drop in Hct was associated with a 2% greater risk of rehospitalization. Golden et al found that 53% of those CHF patients in a heart clinic required hospitalization if their Hct was <35% compared to 21.4% where the initial Hct was ≥ 42%. Uber et al found that 50% of anemic CHF patients required either hospitalization or an emergency room visit compared to only 15% of non-anemics. These findings are consistent with the striking reduction in hospitalization that we found with correction of the anemia in our intervention studies.

The degree of anemia in CHF may also play a role in hospital mortality and hospital costs. A recent analysis of 9107 patients hospitalized with the primary diagnosis of CHF was performed in 21 US hospitals. Hb had an independent effect on in-hospital mortality. Multivariate remodeling showed that a 1-g/dl increase in Hb was associated with a 10.2% reduction in mortality risk, a 5.1% reduction in length of stay and a 5.3% decrease in hospital charges. In another CHF study, Felker et al found that the in-hospital mortality was 6.1% in those with a Hb of ≤ 11.3 g/dl, 2.4% in those with a Hb of 11.4-13.9 g/dl and 1.4% in those with a Hb of >13.9 g/dl. In a trial of ACEI in CHF, the studies of Left Ventricular Dysfunction (SOLVD) trial, Hct levels were significantly related to hospital expenses - the hospital expenses were 19.9% less for an Hct of ≥ 36% compared to an Hct of < 33%.

Effects of anemia on renal function in CHF

Does anemia cause progression of the renal failure in CHF? In a study of 1004 consecutive patients admitted with a primary diagnosis of CHF, anemia was more prevalent in those who experienced a worsening of renal function during admission. In a case control study of some of these same CHF patients, anemia was an independent predictor of worsening of renal function. As in our previous studies, in a recent study of 78 anemic CHF patients, we found that 91.0% of anemic CHF patients when first seen by us in an outpatient setting already had moderate to severe renal failure as defined by a creatinine clearance of < 60 ml/min/1.73 sq m. The mean serum creatinine and creatinine clearance initially were 2.2±0.9 mg/dl and 32.5±26.5 ml/min/1.73 sq m respectively, and these did not change significantly over a mean of 20.7±12.1 months during which the anemia was corrected. It is a striking observation that the renal function in our anemic CHF-CKI patients in all our studies, which had been deteriorating at a rate of about 1 ml/month despite maximal CHF medications when they were anemic, appeared to stabilize in most patients when the anemia was controlled and when the patient received optimal CHF medications in optimal doses. These findings suggest that aggressive and early medical therapy of CHF and correction of the associated anemia may prevent the worsening not only of the CHF but of the CKI as well.

Our findings on renal function are consistent with the effect of anemia correction in CKI without CHF seen in other studies. Anemia in CKI is associated with a more rapid rate of deterioration of renal function than in non anemias and in a recent controlled study of anemia in CKI it was found that that correction of the anemia with EPO could greatly slow down the progression of the renal failure.

A lower hematocrit before or shortly after percutaneous coronary intervention (PCI) has also been found to be an independent and important risk factor for the development of contrast-induced nephropathy, increasing the risk by about 50-100%. Thus it is possible that correction of the anemia with EPO may prevent contrast-induced nephropathy. This clearly deserves a controlled study since contrast-induced nephropathy is a common cause of acute renal failure.

The effect of anemia on other cardiac and non-cardiac conditions

The sensitivity of the damaged heart to anemia has been shown in many animal studies - CHF develops at much milder degrees of anemia in those with damaged hearts than in those with normal hearts. This is consistent with our findings and those of others. For example, as mentioned above, recent studies of patients with CHF show that survival is much worse in the anemic CHF patient than in those with a normal hemoglobin level. Even patients with heart disease but without CHF may be very sensitive to the damaging effects of anemia. In a recent preliminary study, patients who had asymptomatic left ventricular systolic dysfunction without CHF were 2 to 3 times more likely to develop symptomatic CHF, be hospitalized or die over a period of several years if they were also anemic, independent of other factors such as age or renal function. Anemia has also been found to be associated
with markedly reduced survival in patients one month\(^6\)-\(^8\) and one year\(^6\)-\(^9\) after a myocardial infarction (MI). In addition, two years after elective PCI in male patients with proven coronary heart disease (CHD),\(^7\) patients in the lowest Hb quintile showed, in Cox regression analysis, a markedly higher risk for death (adjusted hazard rate ratio of 4.09). Indeed in those CHD patients with an initial Hb of \(\leq 10.9\) g/dl the mortality at 2 years was 55% compared to only 3% in those with a Hb of 14-14.9 g/dl! Remarkably, 48% of all deaths occurred in the lowest Hb quintile which included only 21% of all PCI patients. In 3 other studies of patients with suspected CHD who underwent coronary angiography, anemia was also found to be an independent risk factor for adverse outcomes including death and cardiovascular complications.\(^2\)-\(^4\) All these suggest that anemia may be a common and important contributor to death and morbidity in patients with CHD unrelated to CHF. One study suggests that this anemia may actually be causative of the mortality in CHD and not merely a casual association.\(^5\) In that study correction of anemia by blood transfusion during hospitalization for an acute MI was associated with a marked reduction in the mortality rate over a one month period compared to those anemic patients not transfused. Clearly this field needs more investigation.

The etiology of the anemia in CHF

The main cause of the anemia is most likely renal damage produced by the poor cardiac function. The reduced cardiac output and renal vasoconstriction lead to prolonged renal ischemia. This causes renal damage and reduced production of EPO in the kidneys. However studies in animals have shown that CHF itself may cause anemia.\(^5\) The damaged heart may secrete cytokines such as TNF\(\alpha\)\(^6\)-\(^8\) which can cause anemia in 4 ways\(^9\)-\(^11\); by reducing EPO production in the kidneys, by interfering with EPO activity at the level of the bone marrow, by inhibiting the release of Fe from the reticulo endothelial system so that it cannot get to the bone marrow to be utilized in Hb production, and by reducing iron absorption from the gut. Indeed it has recently been shown that the higher the TNF\(\alpha\) in CHF the lower the Hb level.\(^12\) The reduced iron absorption from the gut is probably due to the release of hepcidin from the liver. This peptide is released by Ile6 and goes to the gut where it prevents the absorption of iron.\(^13\)-\(^16\) We recently found an inhibitor to erythropoiesis that was secreted by cultured rat cardiomyocytes after they were exposed to anoxia for 2 hours (Wollman Y and Fibach E unpublished data). The supernatant fluid was added to cultures of normal human erythroid progenitors and this fluid inhibited these red cell progenitors from multiplying and maturing into hemoglobin-producing red cells. This suggests that the damaged heart cells can indeed produce substances that inhibit erythropoiesis.

There are many other possible causes of anemia in CHF. Many CHF patients take aspirin which may cause blood loss. CHF patients often have proteinuria, and EPO, iron and transferrin can all be lost in significant amounts in the urine also contributing to the anemia. EPO production can be inhibited by ACEIs and ARBs and thus cause anemia.\(^17\)-\(^19\) Indeed in a recent study, the SOLVD randomized controlled study of ACEI in CHF, the use of ACEIs increased the risk of developing anemia by 56% and this was associated with a significant increase in mortality.\(^20\) Over one year the Hct fell by at least 4% in 14% of those taking enalapril but in only 9.5% of those on placebo. The anemia of ACEI is probably due mainly to 1) inhibition of angiotensin II production and to lowering of insulin growth factor levels, both of which can cause inhibition of erythropoietic precursors, and also to 2) an ACEI-induced increase in N acetyl-3-seryl-aspartyl-lysyl proline, a natural peptide that also decreases red cell precursors.\(^21\) As previously mentioned, many patients with CHF have CKI which itself is known to cause reduced iron absorption from the gut.\(^22\) Diabetics are about twice as likely to develop anemia as non diabetics.\(^23\)-\(^25\) This is probably due mainly to the fact that the elevated blood sugar damages the EPO-producing cells in the kidney, lowering the secretion of EPO. However many anemic diabetics also show signs of iron deficiency.\(^26\)-\(^28\) Finally, part of the anemia in CHF may be due to hemodilution, but recent studies showed that the majority of anemic CHF patients actually have a reduced red cell volume.\(^29\)

Iron deficiency in CKI

In the Third National Health and Nutrition Examination Survey (NHANES III) (1988-1994 data), among those with CrCl of 20 to 30 ml/min, 46% of women and 19% of men had iron deficiency as defined by %TSat <20% and 47% of women and 44% of men had it as defined by a serum ferritin <100ug/L.\(^30\) The iron deficiency was independently associated with a lower Hb. Those men with the most severe iron deficiency anemia (as judged by having high erythrocyte protoporphyrin levels) had a mean Hb 1.8 g/dl lower than those with normal erythrocyte protoporphyrin levels, i.e. no iron deficiency. In a subsequent analysis of their data\(^31\) the same investigators found that in the range of CrCl 30-50 ml/min less than one-third of men with a Hb of <12 g/dl and women with a Hb of <11 g/dl had a serum ferritin >100ug/L and a %TSat>20%. In addition, the %TSat above 20% was independently associated with higher Hb levels. All this again suggests that iron deficiency may effect over half the patients with moderate or severe CKI. Several studies have shown that treatment of iron-deficient CKI patients with IV iron even without EPO can cause a substantial increase in the Hb level.\(^32\)-\(^34\)

Attitude of cardiologists and internists to anemia in CHF

In a preliminary report from the Cleveland Clinic,\(^35\) 2011 consecutive ambulatory patients with chronic CHF seen in tertiary care cardiology or internal medicine clinics were studied. Anemia was defined as a Hb <12g/dl in men and <11g/dl in women. 29% of these CHF patients had or developed anemia. Yet anemia was only recognized as a diagnosis in 11.1% of these cases by the internists and in only 4.4% of the cases by cardiologists. Diagnostic evaluation was only performed in 6% of these patients and only 10% received medical therapy for the anemia. The conclusion of the investigators was that anemia in ambulatory patients with CHF was under-recognized, under-diagnosed and under-treated by cardiologists and internists. In another study anemia was found as a physician-recorded diagnosis in 17% of the records of CHF patients\(^36\) but when actual Hb values were examined in the charts of such patients by the same group in another study the prevalence of anemia was actually 38%.\(^37\) Clearly, anemia is often not recognized by physicians as a problem in CHF.
These findings are consistent with recent American guidelines in detection and treatment of CHF which do not mention even a single word about anemia.

Clearly, cooperation must exist between cardiologists and nephrologists in treating these patients' anemia and CHF early and vigorously. Our own program is based on such mutual cooperation.

Non-hematopoietic actions of erythropoietin

EPO modulates a broad array of cellular processes outside of the hematopoietic system including progenitor stem cell development, cellular integrity and angiogenesis. EPO also inhibits the apoptotic mechanisms of injury and inflammatory damage. It may offer protection against several kinds of injury in the heart, the central and peripheral nervous system, the eyes, the kidneys and the blood vessels.

The antioxidant effects of erythropoietin

The improvement in the cardiac function, renal and patient function that we see when the anemia is corrected with EPO may not be related only to the increased oxygen carrying capacity of the blood and the delivery of more oxygen to the tissues. The RBC has many antioxidants which can neutralize the oxidative stress produced by radical oxygen species (ROS) that are produced in excessive amounts in CHF and CKI and can damage all the cells of the body by causing increased collagen synthesis and fibrosis, causing lipid peroxidation, releasing inflammatory cytokines and causing apoptosis of endothelial cells and smooth muscle cells. The neutralization of ROS is produced mainly by the glutathione system in the RBC with enzymes such as superoxide dismutase or catalase which react with the ROS and limit their effect on surrounding tissues. Thus simply increasing the number of erythrocytes can cause a major improvement in oxidative stress.

The vicious circle of CHF, CKI and anemia-the Cardio Renal Anemia (CRA) syndrome

A vicious circle therefore appears to be present in CHF, where CHF itself causes both anemia and CKI. The CKI causes more anemia and the anemia and CKI act back to further worsen the CHF which then further worsens the anemia and CKI and so on. In other words each of the three can cause or be caused by the other. We have suggested calling this relationship the cardio renal anemia (CRA) syndrome.

This vicious circle is caused by over activity of four systems, the sympathetic, RAAS, oxidative stress and inflammatory systems. These not only work together but further stimulate each other. The importance of this concept is that if the anemia is not treated in CHF patients there will likely be resistant to any other form of CHF therapy and there will be progression of both the CHF and the CKI. Thus correction of anemia may be crucial in the prevention of the progression of both CHF and CKI. It also follows that the failing heart needs maximal protection with all the CHF medications in the recommended doses.

The challenge of detecting and treating anemia and CHF in the community

All the above suggests that if CHF is diagnosed early and treated with adequate doses of diuretics, ACE inhibitors (and/or with angiotensin receptor blockers), with those beta blockers that have a proven effect in CHF (Carvedilol, Metoprolol, or Bisoprolol), and, wherever possible, Aldospirone, the resultant control of CHF in the community will be far better than it is today. The evidence is mounting, however, that control of the associated anemia may also be another crucial element in the treatment of CHF. Indeed in our experience the correction of anemia is often associated with a profound improvement in cardiac function, patient function and quality of life in patients who were resistant to all of the usually recommended treatments. In addition, improvement in the Hb and cardiac function may also prevent deterioration of the renal function. This holds out the possibility that control of CHF is an important means of preventing CKI as well.

Conclusion

The use of aggressive therapy of CHF with maximally tolerated doses of CHF medications in combination with anemia correction by subcutaneous erythropoietin and IV iron in patients with the combination of anemia, CHF and CKI was associated with an improvement in CHF, a stabilization of renal function, a low mortality, a reduction in hospitalization and an improvement in quality of life. Close cooperation between nephrologists, cardiologists, diabetologists, internists and family physicians will help maximize the care of these complicated CHF-CKI patients. The benefits to the patients in terms of quality of life, improved physical function, less hospitalizations and avoidance of dialysis and early death make it worth the effort.

References


